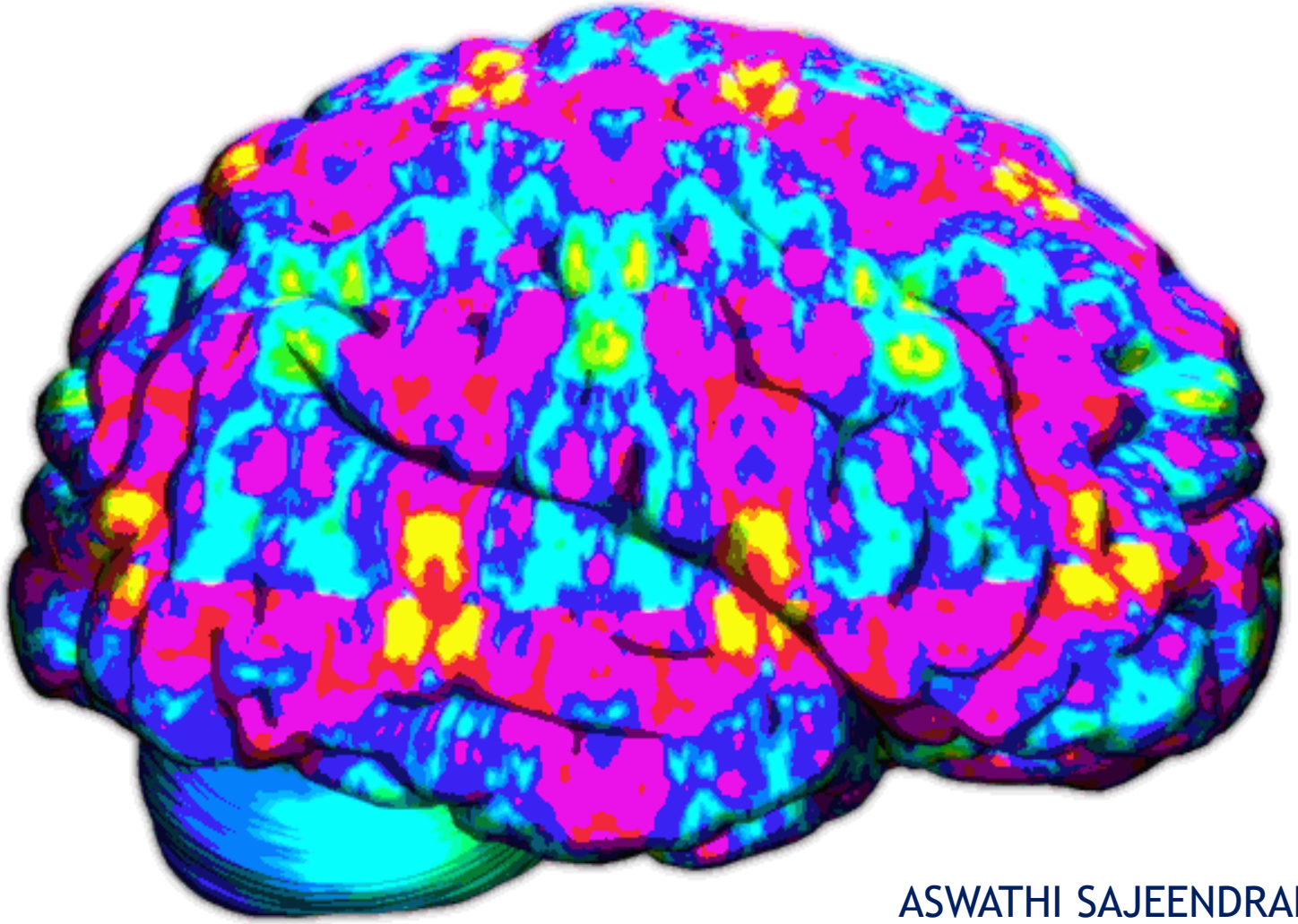
AUTOIMMUNE ENCEPHALITIS



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DEFINITION

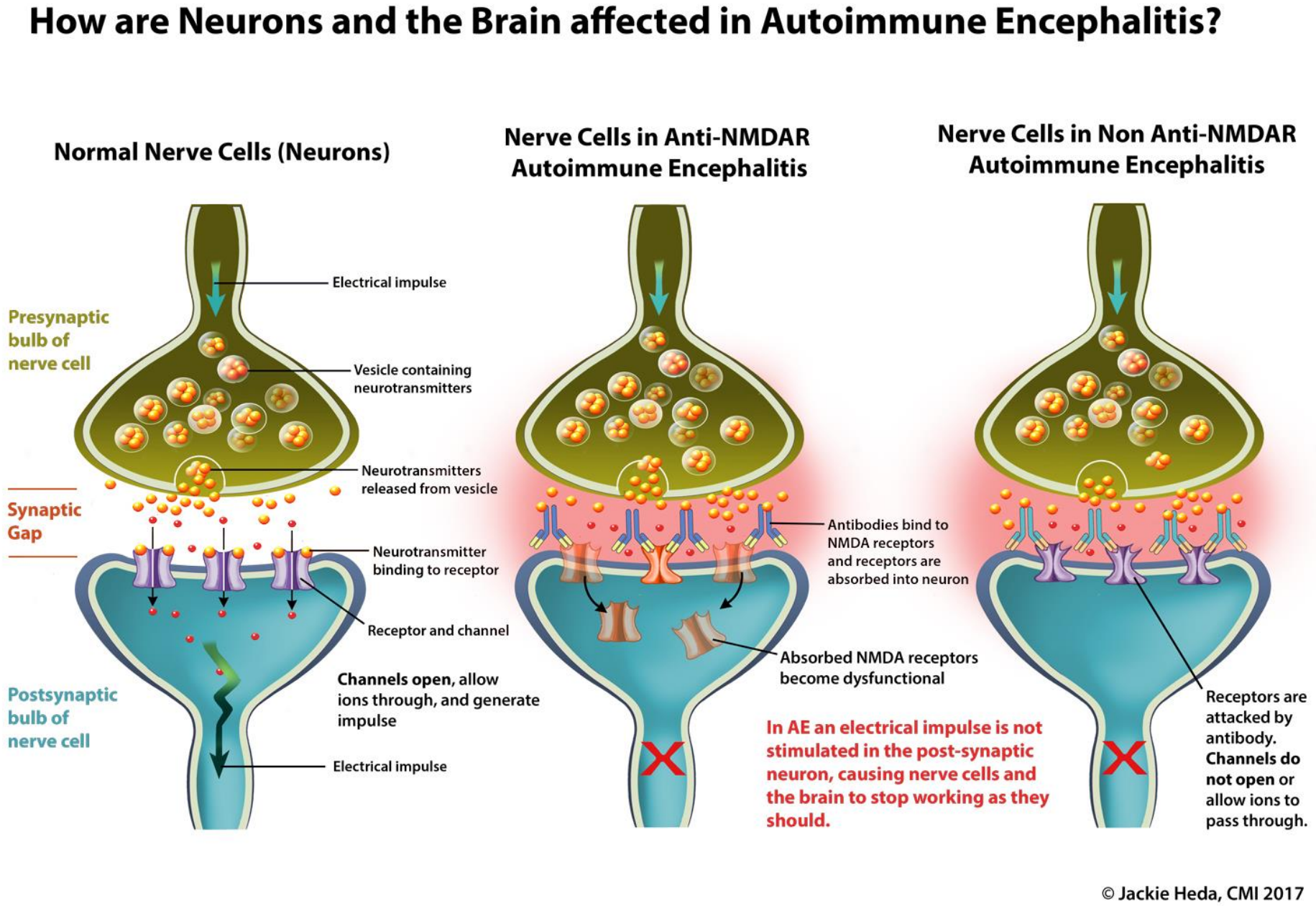
Autoimmune encephalitis (AE) comprises a group of non-infectious immune-mediated inflammatory disorders of the brain parenchyma.

EPIDEMIOLOGY

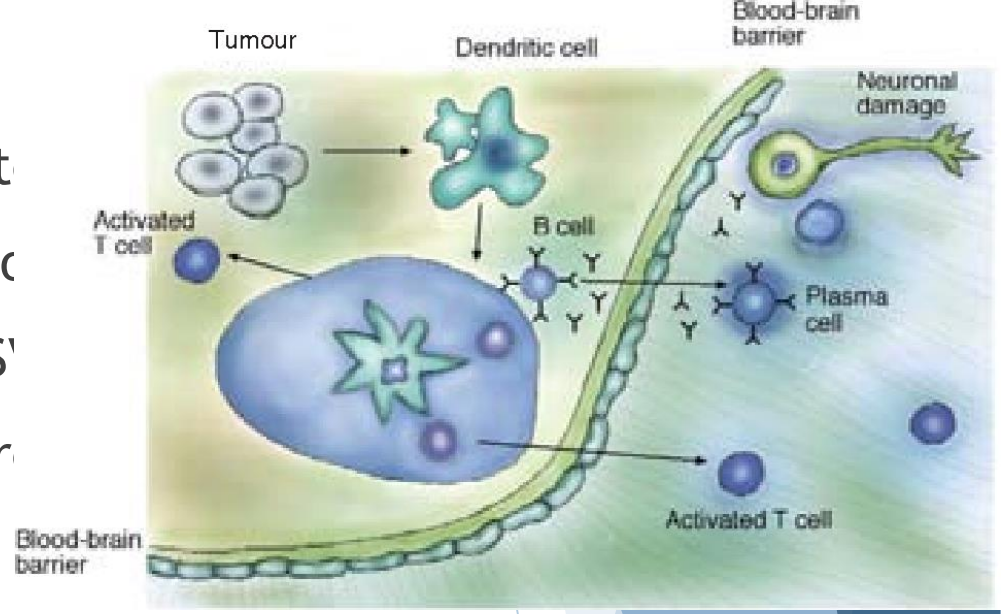
- Estimated prevalence rate of 13.7/100 000.
- The incidence of AE increased from 0.4/100,000 between 1995 and 2005 to 1.2/100,000 between 2006 and 2015 (improved detection of autoantibody-positive cases)
- Male : female = 2.7

ETIOPAT

- Immune resp
  antibodies ar
  1) Antibodies ag
  receptor, Glycin
  2)Antibodies ag
  3) Antibodies ag
  - ANNA-1/anti-
  - PCA1/Anti-Yo
  - PCA – Tr / DN
  - Anti-Ma (Test
- Can occur wi
  encephalitis)



- Cell surface and synaptic antibodies have been shown t
  pathogenic and are thought to be immunotherapy-respc
  have less association with tumours. Viral infections (HS
  triggers . Eg- Antibodies against NMDAR, dopamine D2 r
  receptor and other synaptic proteins



- Onconeural antibodies are non-pathogenic but represent markers of T-cell-mediated immunity against the neoplasm with secondary response against the nervous system. Antibodies are 70% sensitive and 80-90% specific for paraneoplastic AE, and does not correlate with disease severity.
- Seronegative AE represents a disease category with novel, yet to be identified antibodies or T-cell mediated disease.

CLINICAL FEATURES

- Rapidly progressive dementia
- Psychiatric symptoms – hallucinations, psychosis
- Seizures
- Movement disorders : ataxia, dystonia, myoclonus, and orofacial dyskinesia (NMDAR)
- Faciobrachial dystonic seizures, hyponatremia (LGI 1)
- Sleep disorders (insomnia, sleep-wake cycle disturbance), peripheral nerve hyperexcitability (CASPR2)
- Autonomic disturbances
- Gastrointestinal manifestations -diarrhea, gastroparesis, and constipation (DPPX)

Targeting antigen	Clinical features or main syndrome	Tumor associations
Intracellular cytoplasmic antigens		
ANNA-1 (anti-Hu)	Encephalomyelitis (cortical, LE, BSE), cerebellar degeneration, sensory neuropathy, autonomic dysfunction	SCLC, other
ANNA-2 (anti-Ri)	Cerebellar degeneration, BSE, opsoclonus-myoclonus	Breast, gynecologic, SCLC
Anti-Ma (Ma1, Ma2)	LE, BSE, peripheral neuropathy, hypothalamic dysfunction	Testicular cancer, lung cancer, other solid tumors
Anti-CRMP-5	Encephalitis, optic neuritis, retinitis, myelopathy, Lambert-Eaton myasthenic syndrome	SCLC, breast cancer
Anti-amphiphysin	Stiff-person syndrome, LE	Breast, lung cancer
Anti-GAD65	LE, stiff-person syndrome, BSE, cerebellar ataxia, diabetes, ocular movement disorder	Thymoma, renal cell, breast, or colon cancer
Plasma membrane antigens		
Synaptic receptors		
NMDAR	Psychosis, insomnia, seizures, behavior change, memory impairment, autonomic dysfunction, catatonia, coma	Age-dependent ovarian teratoma
GABAA receptor	Rapid progressive encephalopathy, refractory seizures, status epilepticus	40% (thymoma)
GABAB receptor	Prominent seizures, LE, cerebellar ataxia, opsoclonus-myoclonus	50% (mostly SCLC)
AMPA receptor	LE, psychiatric disturbances, memory loss	Thymoma, SCLC
GlyR	LE with status epilepticus, encephalomyelitis, muscle spasm, rigidity, hyperekplexia	Past history of cancer, concurrent cancer

mGluR5	Confusion, encephalitis (Ophelia syndrome)	Hodgkin lymphoma
mGluR1	Cerebellar ataxia	Hodgkin lymphoma
Dopamine-2 receptor	Basal ganglia encephalitis	No
Ion channels and/or cell surface		
LGI1	LE, seizures, FBDS, rapidly progressive cognitive decline, hyponatremia	Thymoma (5%-10%), hyponatremia (60%)
Caspr2	Insomnia, Morvan syndrome, peripheral nerve hyperexcitability (neuromyotonia), LE, neuropathic pain, autonomic dysfunction, ataxia	Thymoma, variable solid tumors
DPPX	Encephalopathy, hyperexcitability, myoclonus, tremor, diarrhea, weight loss	Lymphoma
MOG	Acute disseminated encephalomyelitis	No
Aquaporin 4	Encephalitis, neuromyelitis optica	No
GQ1b	BSE	No

AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ANNA-1, antineuronal nuclear antibody type 1; LE, limbic encephalitis; BSE, brainstem encephalitis; SCLC, small-cell lung cancer; CRMP-5, collapsing response mediator protein-5; GAD, glutamic acid decarboxylase; NMDA, N-methyl-D-aspartate; GABA, γ-aminobutyric acid; GlyR, glycine receptor; mGluR, the metabotropic glutamate receptor; LGI1, leucine-rich glioma inactivated-1; FBDS, faciobrachial dystonic seizures; Caspr2, contactin-associated protein-like 2; DPPX, dipeptidyl-peptidase-like protein; MOG, myelin oligodendrocyte glycoprotein.

Anti-NMDAR encephalitis

- Predominantly affects children and young female patients (12-45 years of age)
- Commonly associated with ovarian teratoma (94%), followed by extraovarian teratomas (2%), and other tumors (4%). Herpes simplex virus-1 encephalitis appears to be a trigger for anti-NMDAR encephalitis.
- Patients may progress from behavioural changes to catatonia or mutism, so an important differential diagnosis of anti-NMDAR encephalitis is neuroleptic malignant syndrome, because many patients are initially treated with neuroleptics for behavioral symptoms

R2 encephalitis

ncephalitis

omyotonia, pain, hyperhydrosis, weight loss,

bic encephalitis

eracts with transmembrane proteins ADAM22

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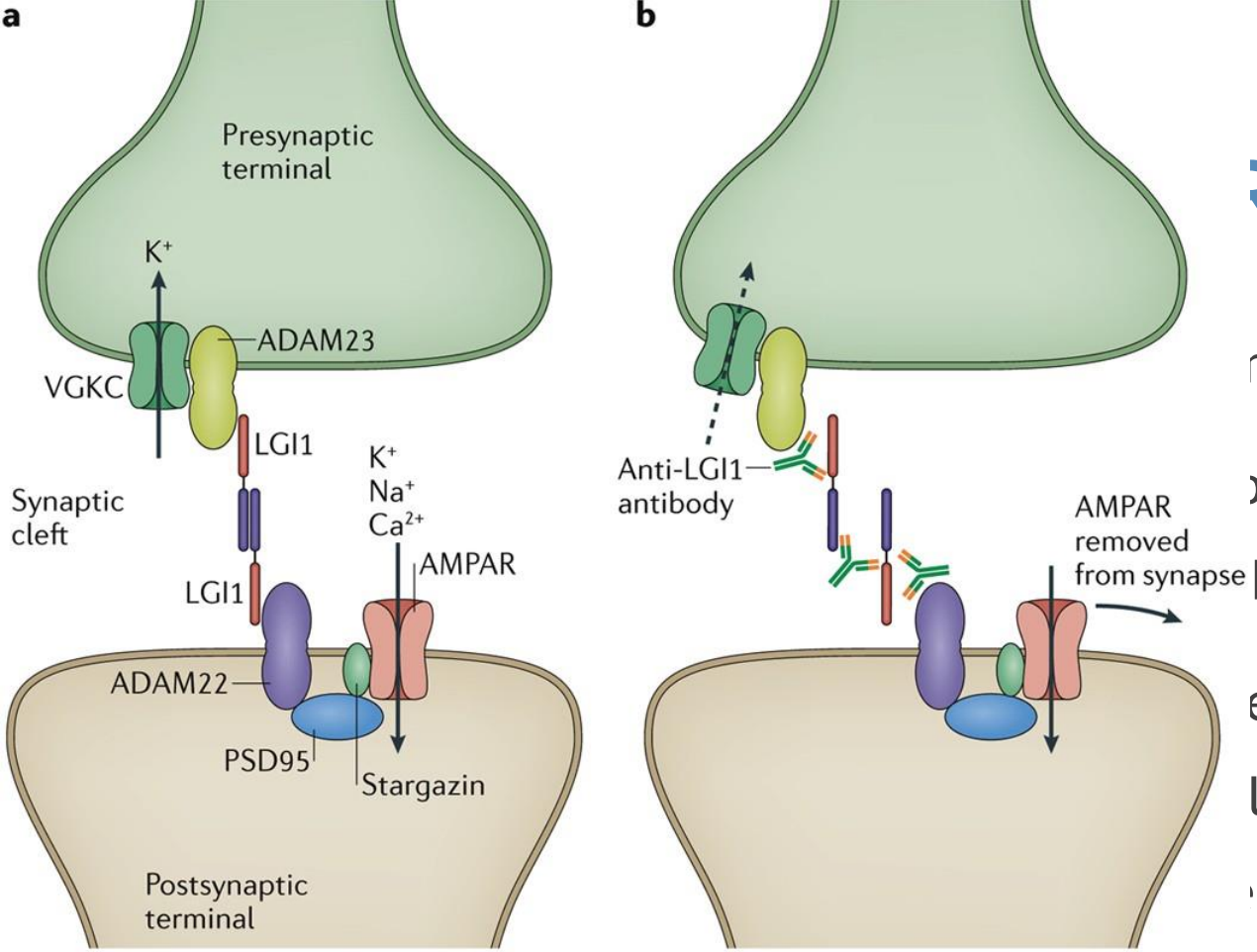

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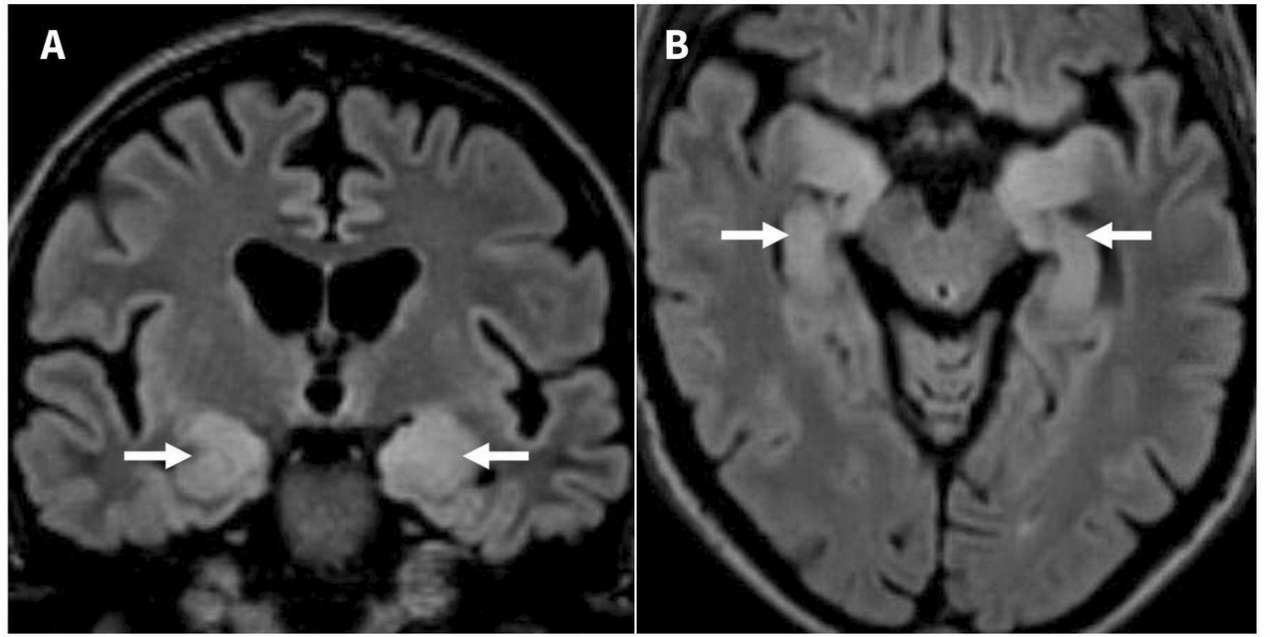

seizures, which are characterized by brief u

evolving into the ipsilateral face or leg) last

day. Most patients present with brain MRI hy

Anti-GAD encephalitis

- Glutamic acid decarboxylase (GAD) is an enzyme that catalyzes the conversion of glutamic acid to the neurotransmitter GABA
- Stiff-person syndrome, cerebellar ataxia, epilepsy and limbic encephalitis
- Stiff-person syndrome - muscle stiffness resulting from co-contractions of agonist and antagonist muscles, painful spasms and pronounced startle responses.

Anti-DPPX encephalitis

- DPPX is a subunit of potassium channels expressed in the hippocampus, cerebellum, striatum, and myenteric plexus.
- Neuropsychiatric symptoms (agitation and confusion), myoclonus, tremor, startle reflex, seizures, stiff-person syndrome
- Prominent GI symptoms –diarrhea and weight loss preced neurological symptoms
- Good response to immunotherapy

Box 1. Diagnostic criteria for possible autoimmune encephalitis[6]

Diagnosis can be made when all three of the following criteria have been met.

- Subacute onset (rapid progression of less than 3 months) of working memory deficits (short-term memory loss), altered mental status or psychiatric symptoms.
- At least one of the following:
  - new focal CNS findings
  - seizures not explained by a previously known seizure disorder
  - CSF pleocytosis
  - MRI features suggestive of encephalitis.
- Reasonable exclusion of alternative causes (eg HSV encephalitis).

CNS = central nervous symptoms; CSF = cerebrospinal fluid; MRI = magnetic resonance imaging.

DIAGNOSIS

- MRI of the brain
- EEG – non- specific
- Blood tests- for autoantibodies; rule out in
- CSF- Lymphocytic pleocytosis
- Screen for tumors at disease onset (CT of t
  MRI for breast cancer, ultrasound followed
- If initial tumor screening is negative but th
  paraneoplastic (e.g. anti-NMDAR in young a
  anti-GABA-BR), screening should be repeat
  screenings every six months for four years

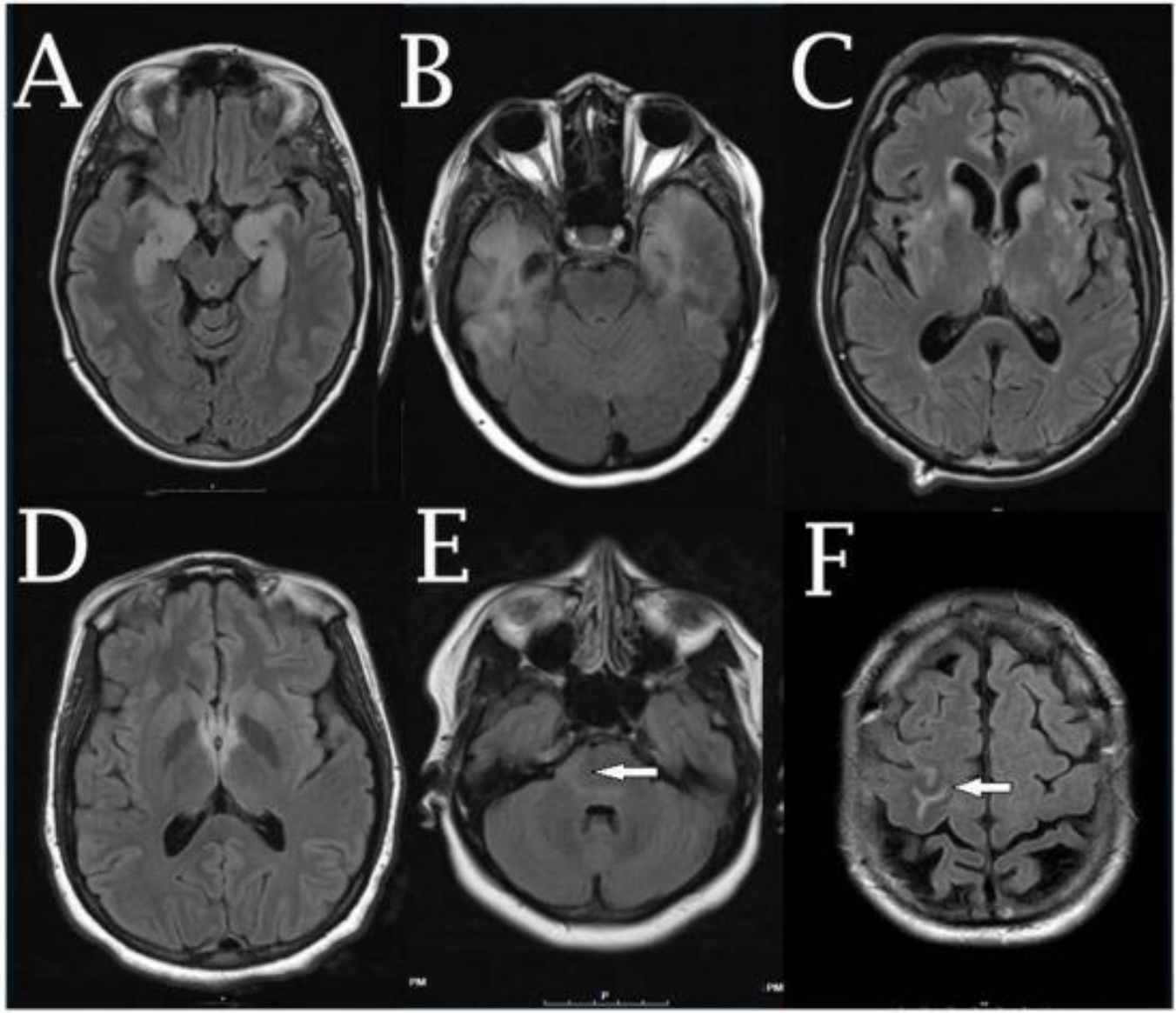

Figure 3 Anatomical subtypes of autoimmune encephalitis. (A) Limbic encephalitis, (B) cortical/subcortical encephalitis, (C) striatal encephalitis, (D) diencephalic encephalitis, (E) brainstem encephalitis (arrow), (F) meningoencephalitis (arrow).

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TREATMENT

PARANEOPLASTIC

- Aggressive cancer treatment and immunosuppression
- Poor prognosis; usually irreversible neuronal damage

NON PARANEOPLASTIC

- Steroids, IvIG, Plasma exchange
- Immunomodulators : Mycophenolate, Rituximab, Alemtuzumab, Natalizumab, Tocilizumab, Eculizumab

DIFFERENTIAL DIAGNOSIS

- FTD/ Alzheimer Disease
- Prion disease - CJD
- Psychiatric disorders – Depression, pseudodementia, schizophrenia
- CVA/ CNS vasculitis
- Tumours , Primary CNS Lymphoma
- Infection - HIV, HHV-6-associated encephalitis
- ADEM
- NMOSD
- Neuropsychiatric lupus

THANK YOU